Synopsis XM22-03

Name of Sponsor/Company: now owned by Teva	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: XM22 Drug Product	Volume:	
Name of Active Ingredient: glycol-PEGylated-r-metHuG-CSF (INN; Code: XM22)	Page:	

Title of Study: Efficacy and safety of XM22 compared to pegfilgrastim in patients with breast cancer receiving chemotherapy (multinational, multicentre, randomised, double-blind controlled study)

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Investigators: Please refer to list of investigators (refer to: *Appendix 16.1.4*).

Study centres: Patients were screened at 27 centres in 2 European countries. Patients were randomised in 27 centres (Russia 15, Ukraine 12).

Publication (reference): Not applicable

Studied Period:	Date of first patient enrolled: 18 May 2010 Date of last patient completed:09 December 2010
Phase of development:	III

Objectives:

Primary: The primary objective of this study was demonstration of non-inferiority of XM22 versus pegfilgrastim (Neulasta ®) in patients with breast cancer during the first cycle of chemotherapy with respect to the duration of severe neutropenia (DSN), defined as grade 4 neutropenia with an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L.

The secondary objectives of this study were demonstration of efficacy and safety of XM22 in comparison to pegfilgrastim in patients with breast cancer under chemotherapy based on the secondary efficacy and safety endpoints and evaluation of pharmacokinetic properties of XM22 in comparison to pegfilgrastim.

Methodology: This study was a multinational, multicentre, randomised, double-blind, controlled, phase III study. A total of 200 patients with high-risk stage II, III, or IV breast cancer needing chemotherapy (CTX) were to be randomised to double-blind treatment with either 6 mg XM22 (n = 100) or 6 mg Neulasta® (n = 100).

The patients were to undergo a maximum of 4 CTX cycles (3 weeks per cycle), each cycle beginning on the day of CTX (day 1). In order to be eligible for randomisation at the baseline visit on day 1, ANC and platelet values had to be above the defined limits (ANC $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L).

All randomised patients were to receive myelosuppressive CTX on day 1 of each cycle (60 mg/m^2 doxorubicin as an i.v. bolus injection followed by 75 mg/m^2 docetaxel as an i.v. infusion over at least 1 hour administered 1 hour later). Study drug (6 mg XM22 or 6 mg Neulasta®) was to be given as an s.c. injection on day 2, approximately 24 hours after start of CTX. CTX was repeated every 3 weeks (unless a dose delay was necessary) for a maximum of 4 cycles. To begin full dose CTX on day 1 of each subsequent cycle, the patient had to have recovered to an ANC of $\geq 1.5 \times 10^9$/L and a platelet count of $\geq 100 \times 10^9$/L. A delay of the subsequent cycle for up to 14 days was acceptable.

Number of patients (planned and analysed): It was planned to randomise 100 patients per group for a total of 200 patients to allow demonstration of the non-inferiority of XM22 with Neulasta®. 101 patients were randomised and treated in each treatment group; 202 patients in total.

Diagnosis and main criteria for inclusion: Female or male patients were to have breast cancer high risk stage II, III or IV receiving docetaxel/doxorubicin as routine chemotherapy. Patients were to be CTX-naïve with ANC $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. ECOG performance status was to be ≤ 2 and cardiac, hepatic and renal function was to be adequate.

Test product, dose and mode of administration, batch number: XM22 was supplied in pre-filled syringes containing 0.6 mL for s.c. injection.

Patients were to receive a single dose of 6 mg as a subcutaneous injection once per CTX treatment cycle.

Batch numbers XM22: XM22-03/01 and XM22-03/04

Duration of treatment: Patients were treated for 12 weeks. Thereafter the patients were observed for adverse events for 30 days after the last administration of study medication.

Reference therapy, dose and mode of administration, batch number: Neulasta ® was supplied in 0.6 mL (10 mg/mL) pre-filled syringes for s.c. injection.

Patients were to receive a single dose of 6 mg as a subcutaneous injection once per CTX treatment cycle.

Batch numbers Neulasta ®: 1016587 and 1015991

Criteria for evaluation:

Primary endpoint for efficacy: The primary efficacy endpoint was defined as the DSN in cycle 1. Severe neutropenia was defined as grade 4 neutropenia (ANC <0.5 x 10^9/L).

Secondary endpoints for efficacy:

- Incidence of febrile neutropenia in cycles 1, 2, 3, and 4 and across all cycles.
- DSN in cycles 2, 3, and 4.
- Depth of ANC nadir in cycles 1, 2, 3, and 4.
- Time to ANC nadir.
- Time to ANC recovery in cycles 1, 2, 3, and 4.
- Time to ANC recovery from ANC nadir in cycles 1, 2, 3, and 4.
- Incidence of grade 4 neutropenia (ANC <0.5 x 10^9/L) and of very severe neutropenia (ANC <0.1 x 10^9/L) in cycles 1, 2, 3, and 4.
- Duration of very severe neutropenia in cycles 1, 2, 3, and 4.
- Hospitalisation and Intensive Care Unit; Incidence of treatment with i.v. antibiotics; CTX intensity and density
- Overall quality of life

Safety

- Incidence of adverse events (AEs).
- AEs of special interest
- Changes in safety laboratory parameters.
- Changes in vital signs, physical examination and body weight.
- Electrocardiogram (ECG) (sub-study)
- Assessment of injection site reactions.
- Immunogenicity (development of antibodies against study drug).
- Mortality
- Frequency of culture-confirmed infections.
- Frequency of neutropenic fever.
- Number of transfusions and/or use of erythropoietin or erythropoietin releasing agents.

Other

- Pharmacokinetics in a subset of patients.
- CD34+ cell mobilisation in a subset of patients.

Statistical methods: All efficacy analyses were performed with the data of the Intent-to-treat (ITT) population, i.e. all patients who were randomised to one of the treatment groups and the According-to-protocol (ATP) population, which consisted of all patients from the ITT population without a major protocol violation. The primary population for the analysis of efficacy in this non-inferiority trial was the ATP population. The robustness of the results in the ATP population were supported by the ITT population.

The primary objective was the demonstration of non-inferiority of XM22 versus pegfilgrastim (Neulasta ®) in patients with breast cancer. The primary efficacy endpoint was defined as the DSN in cycle 1. Severe neutropenia was defined as grade 4 neutropenia (ANC $<0.5 \times 10^9$/L).

DSN was calculated as the sum of all days after CTX (day 2 to 21, or if for a patient ANC measurements after day 21 were available, until the last available ANC measurement) with ANC $<0.5 \times 10^9$/L.

For the analysis of the primary efficacy endpoint, a Poisson regression with identity link was applied including "treatment", country, kind of therapy, and body weight as fixed factors, and with the last ANC value measured prior to start of the study treatment (baseline ANC) as covariate. The model also included a provision for possible overdispersion.

Where applicable, for secondary efficacy endpoints for which regression analyses were planned in the study protocol, the statistical models included the same explanatory variables as for the main efficacy endpoint.

The population for analysis of safety data was the safety population which is identical to the ITT population in this study.

Demographic and baseline characteristics, AEs and other safety endpoints were presented as descriptive statistics (continuous variables) or frequency tables (categorical variables).

Summary – Conclusions

The demographic and baseline characteristics of the ITT population were comparable across both treatment groups. Mean (± SD) age was comparable in both groups (51.1 (± 9.4) years for Neulasta ® vs.49.9 (± 10.1) years for XM22) and was typical of the target patient population (breast cancer patients receiving CTX). All patients were Caucasian women.

Efficacy Results:

Primary Endpoint

The DSN in cycle 1 was comparable in both treatment groups, with a mean (SD) DSN in the ATP population of 0.8±0.9 days in the Neulasta ® group and 0.7±0.9 days in the XM22 group. Poisson regression analysis (XM22 - Neulasta ®) yielded a 95% CI of -0.498 to 0.062 with p=0.1260. Non-inferiority of XM22 versus Neulasta ® during the first cycle of chemotherapy with respect to the DSN was therefore demonstrated (the upper limit of the 2-sided 95% CI is less than 1).

Secondary Endpoints

All p-values reported for the comparison of treatment groups concerning the secondary efficacy endpoints are raw and unadjusted p-values of explorative tests on differences between treatments.

The DSN in each cycle was comparable in the 2 treatment groups with no statistically significant differences observed. As expected, the mean DSN was consistently shorter in cycles 2 to 4 than in cycle 1 in both treatment groups. Of note, in each of cycles 2 to 4 over 75% of the patients in each treatment group experienced no severe neutropenia at all.

In the ATP population only 3 patients had investigator-assessed febrile neutropenia (FN) during the study. All 3 cases occurred in the Neulasta® group during cycle 1, with no FN cases in the XM22 group.

Cycle 1 was the study period with the highest incidences of severe neutropenia (51.1% Neulasta® patients, 43.6% XM22 patients; p=0.3409). Although differences in severe neutropenia between the treatment groups were observed, particularly in cycle 2 (21.5 vs.8.5%; p=0.0130), the incidence of severe neutropenia in the XM22 group was either comparable to or lower than the incidence in the Neulasta® group in each cycle.

The incidence of very severe neutropenia over all cycles was low in both groups (11.7% Neulasta® patients, 6.4% XM22 patients; p=0.2066). As for other neutropenia efficacy variables, cycle 1 was the study period with the highest incidences of very severe neutropenia. Although some differences between the treatment groups were observed, the incidence of very severe neutropenia in the XM22 group was either comparable to or lower than the incidence in the Neulasta® group in each cycle. The duration of very severe neutropenia (DVSN) in each cycle was very short (≤0.1 day) in both treatment groups with no statistically significant differences observed between the groups.

The depth of ANC nadir in both treatment groups was lowest (i.e. worst) in cycle 1 and then increased to 2.0 x 10^9/L or above in cycles 2 to 4. The depth of ANC nadir in cycle 1 was comparable in both treatment groups, with p=0.2539. In cycles 2, 3 and 4, the mean depth of ANC nadir had higher absolute values (i.e. better values) in the XM22 group compared to the Neulasta® group (2.6 vs.2.0, 2.5 vs.2.0, and 2.7 vs.2.3 10^9/L), with p=0.0189, p=0.0353 and p=0.1122, respectively. Therefore, although some differences between the treatment groups were observed in cycles 2, 3, and 4, the differences were consistently in favour of XM22 treatment. The time to ANC nadir was comparable in the treatment groups in each cycle.

The time to ANC recovery in both treatment groups was highest in cycle 1. In cycles 1, 2, and 3, the time to ANC recovery was shorter for XM22-treated patients than for Neulasta®-treated patients, with $p<0.05$ in each case; a shorter time to ANC recovery is better for a patient. In cycle 4, the time to ANC recovery was comparable in both treatment groups.

The time to ANC recovery from ANC nadir in both treatment groups was highest in cycle 1. In all cycles, the time to ANC recovery was shorter for XM22-treated patients than for Neulasta®-treated patients, although $p<0.05$ was only observed in cycle 3; a shorter time to ANC recovery from ANC nadir is better for a patient.

In the ITT population, 2 patients in the Neulasta® group and 1 patient in the XM22 group were hospitalised due to FN or infection. All 3 patients were hospitalised during cycle 1 (one Neulasta® patient for 6 days and the other for 5 days, but not in the intensive care unit (ICU); the XM22 patient for 1 day in the ICU) and received antibiotics; the XM22 patient also received antipyretics. One other patient in the Neulasta® group required antibiotics due to FN in cycle 1 but was not hospitalised.

No clinically relevant differences between the groups were noted for the density and intensity of chemotherapy. The majority of patients in both treatment groups received chemotherapy as scheduled, with the mean percentage of doxorubicin and docetaxel actually applied reaching over 98% in each group in each cycle.

For the EORTC QLQ-C30 and QLQ-BR23 assessments of Quality of Life (QoL), no relevant differences between the treatment groups were observed. The results generally indicated some deterioration in patients' QoL over the course of the study, which is not unexpected in cancer patients undergoing chemotherapy.

The results for the analyses of secondary efficacy endpoints were consistent with those of the primary endpoint, with XM22 demonstrating comparable efficacy to Neulasta®. Where differences between the groups were observed, the difference was consistently due to a greater anti-neutropenic activity for XM22 compared to Neulasta®.

The analysis of efficacy variables in subgroups revealed no relevant differences between the treatment groups or between subgroups.

For all efficacy analyses, the results in the ITT population were consistent with those in the ATP population demonstrating the robustness of the results.

Pharmacokinetics and CD34+ cell mobilisation

The pharmacokinetics of 6 mg XM22 and 6 mg Neulasta® after s.c. administration were similar in many respects.

A key aspect of pharmacokinetics that differed between XM22 and Neulasta® was the AUC in cycle 1. In cycle 1, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were higher for XM22 compared to Neulasta. In cycle 1, the geometric mean of the $AUC_{0\text{-last}}$ was higher for XM22 (14157 h*ng/mL) compared to Neulasta® (10532 h*ng/mL). In cycle 1, the geometric mean of the $AUC_{0\text{-inf}}$ was higher for XM22 (14184 h*ng/mL) compared to Neulasta® (10554 h*ng/mL). Given that both AUC parameters were almost 50% higher for XM22 compared to Neulasta® in cycle 1, the potency of 6 mg XM22 would be expected to be greater than that of 6 mg Neulasta®. This is consistent with the efficacy and safety results observed in this study, with somewhat higher activity observed for XM22 in terms of anti-neutropenic effect and G-CSF-related side effects.

This picture is paralleled by results of CD34+ cell mobilisation, which indicated a trend towards higher cell counts in cycle 1 after treatment with XM22 compared with Neulasta®.

Safety Results (Safety population):

Treatment-emergent AEs (TEAEs) were experienced by 99 (98.0%) patients in the Neulasta ® group and by 100 (99.0%) patients in the XM22 group. This high incidence of TEAEs was to be expected in breast cancer patients receiving CTX.

The most commonly reported events by preferred terms (PTs) (incidence ≥10% in either treatment group) across all cycles were: alopecia (85.1% Neulasta ®, 92.1% XM22), nausea (51.5%, 60.4%), asthenia (28.7%, 27.7%), neutropenia (31.7%, 25.7%), bone pain (9.9%, 13.9%), erythema (11.9%, 11.9%), leukopenia (7.9%, 11.9%), diarrhoea (11.9%, 9.9%). Alopecia, nausea, asthenia, diarrhoea, neutropenia, and leukopenia are known to be associated with the CTX or the underlying disease. Bone pain and erythema are known to be common undesirable effects related to treatment with G-CSF.

Frequencies of PTs were generally comparable between the treatment groups. The only PTs that differed in frequency by ≥5% between the treatment groups were: alopecia (85.1% Neulasta ®, 92.1% XM22), nausea (51.5%, 60.4%), neutropenia (31.7%, 25.7%), and vomiting (4.0%, 9.9%). These differences were not considered to be clinically relevant.

As expected, there was a time-dependent trend across the cycles within each treatment group, i.e. the frequencies of TEAEs decreased across all cycles in both treatment groups.

Severe TEAEs were reported in 35 (34.7%) Neulasta ® patients and 26 (25.7%) XM22 patients. Severe TEAEs occurring in more than 1 patient in a treatment group were neutropenia, alopecia, leukopenia, febrile neutropenia, and anaemia. All of these severe TEAEs are expected in cancer patients receiving CTX.

Treatment-emergent adverse drug reactions (TEADRs, i.e. considered related) were reported in 26 (25.7%) patients in the Neulasta ® group and in 28 (27.7%) patients in the XM22 group. The most common TEADRs observed in this study – bone pain, myalgia, and erythema – are known side effects of G-CSF treatment. TEADRs of bone pain, myalgia, erythema and arthraliga were slightly more frequent in XM22 patients compared to Neulasta ® patients. Severe TEADRs were reported in 2 Neulasta ® patients (neutropenia and tachycardia paroxysmal) and 1 XM22 patient (epistaxis).

A single patient (66 years old), treated with XM22, died in this study. An autopsy proved enterocolitis as the cause of death. Enterocolitis (Grade 4) was documented by the investigator as an additional SAE, assessed as life-threatening, important medical event with outcome death and with no relationship to the study medication.

Serious TEAEs were reported in 7 (6.9%) Neulasta ® patients and in 3 (3.0%) XM22 patients. Febrile neutropenia (2 Neulasta ® patients, 1 XM22 patient) was the only serious TEAE that occurred in more than 1 patient in a treatment group.

Bone-pain-related symptoms were reported in 17 (16.8%) Neulasta ® patients and in 24 (23.8%) XM22 patients. The higher incidence of bone-pain-related symptoms in the XM22 group compared to Neulasta® was reflected in the higher incidence for the PTs bone pain (9.9% Neulasta ® patients, 13.9% XM22 patients), myalgia (5.9%, 8.9%), and arthralgia (2.0%, 5.0%). Although bone-pain-related symptoms were more common in the XM22 group, these

events are expected under G-CSF treatment and were well managed using standard analgesics or required no additional treatment; none of the AEs in bone-pain-related symptoms led to discontinuation of study participation and none were serious; all were mild or moderate in severity.

Overall, results for laboratory safety variables, vital signs (blood pressure and heart rate), body weight, physical examination, infections, febrile neutropenia and blood transfusions, injection site reactions, and concomitant medications did not give rise to any safety concerns.

Changes over time in clinical chemistry and haematology variables were consistent with the underlying disease and the CTX treatments received during the study and the expected effect of G-CSF treatment. Differences between the treatment groups were mostly small and not statistically significant. For alkaline phosphatase (AP) and lactate dehydrogenase (LDH), a higher proportion of patients in the XM22 group had values above the upper limit of normal compared to Neulasta ® group. Reversible mild to moderate elevations in AP and LDH are common side effects of Neulasta ®.

XM22 and Neulasta ® appear to have no effect on ECG parameters, based on the results of the ECG sub-study, except for a comparably low prevalence of nonspecific ST-T changes and a comparable increase in QTcF (cardiac repolarization) in the 10-15 ms range, which may be clinically relevant and was seen in both treatment groups. The concomitant medication common to both treatment groups have known cardiotoxicity and may have caused the ECG changes. .

Conclusion

The primary objective of this study was met: non-inferiority of XM22 versus Neulasta ® during the first cycle of chemotherapy with respect to the DSN was demonstrated.

The results for the analyses of secondary efficacy endpoints were consistent with those of the primary endpoint, with XM22 demonstrating comparable efficacy to Neulasta ®. Where differences between the treatment groups were observed, the differences were due to a greater anti-neutropenic activity for XM22 compared to Neulasta ®.

XM22 had a favourable safety profile. Although typical G-CSF bone-pain-related symptoms were more common in patients treated with XM22 compared to those treated with Neulasta ®, these side effects could be well managed using standard analgesics and did not lead to early discontinuation of study treatment.

Pharmacokinetics and CD34+ cell mobilisation results were consistent with the efficacy and safety results, with XM22 and Neulasta ® exhibiting generally similar profiles but with a higher concentration (in terms of area under the curve) of XM22 in cycle 1 compared to Neulasta ® and somewhat greater CD34+ cell mobilisation.

XM22 is a safe and effective treatment for reducing the DSN in breast cancer patients receiving myelosuppressive CTX.

Date of report Version 2.0 – 21 October 2011